Epitomes

Important Advances in Clinical Medicine

Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in neurology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association and the summaries were prepared under its direction.

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Botulinum Toxin Therapy for Torticollis

BOTULINUM TOXIN has been used for some years to treat ophthalmologic conditions such as strabismus and blepharospasm in which there is inappropriate or unbalanced muscle activity. The toxin binds rapidly and with high affinity to nerve terminals, so that small amounts injected locally into overactive muscles produce focal weakness without causing any serious systemic side effects.

Recent studies have focused on the role of botulinum toxin in the treatment of spasmodic torticollis and other dystonic disorders. In torticollis, which is usually idiopathic and attributed to basal ganglia dysfunction, there is an abnormal posture of the head due to the overactivity of certain neck muscles. Most of the drugs that have been used in its treatment are of limited usefulness, producing either little or no benefit or mild benefit at the expense of side effects that are often distressing. Accordingly, there have now been several trials of using botulinum toxin to treat torticollis. In general, these studies have shown that compared with placebo, botulinum toxin administered to overactive cervical muscles can produce subjective improvement in between 50% and 80% of patients. The benefit may involve both a reduction in abnormal movements or postures and a reduction in pain. Objective benefit may also occur but is more difficult to show, probably because of the insensitivity of the objective rating scales that are available. The benefit may last for several months but eventually wanes unless the muscles are reinjected with the toxin.

Overactive muscles can be injected either in the motor end-plate region or at sites distributed throughout the length of the muscle, with similar results. Various doses have been used in the different published studies but usually are less than a total of 300 units at any one time or 180 units to any single muscle. The estimated median lethal dose for humans is 2,500 to 5,000 units.

Side effects are typically minor and short-lived and include local pain or discomfort about the site of injection, neck weakness, malaise, and occasionally dysphagia (which may last for a few days). The cause of the dysphagia is not clear but may relate to a local spread of the toxin to the muscles of deglutition. There is neurophysiologic evidence that local injections of botulinum toxin produce subtle effects on neuromuscular transmission at distant sites, but these effects are not detectable clinically with the usual doses administered for torticollis.

In some patients, botulinum toxin injections are only briefly effective despite a persistent relaxation of previously overactive muscles, suggesting that the pattern of muscle activity in torticollis may change after botulinum toxin injections, just as it may change following surgical procedures such as rhizotomy, peripheral nerve section, or muscle section. Botulinum toxin therapy for torticollis is now being used at several major medical centers, but the toxin is not yet approved by the Food and Drug Administration for general use.

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REFERENCES

Brin MF, Fahn S, Moskowitz CB, et al: Localized injections of botulinum toxin for the treatment of focal dystonia and hemifacial spasm. Adv Neurol 1988; 50:599-608

Gelb DJ, Lowenstein DH, Aminoff MJ: A controlled trial of botulinum toxin injections in the treatment of spasmodic torticollis. Neurology 1989; 39:80-84

Jankovic J, Orman J: Botulinum A toxin for cranial-cervical dystonia: A double-blind, placebo-controlled study. Neurology 1987; 37:616-623

Tsui JK, Fross RD, Calne S, et al: Local treatment of spasmodic torticollis with botulinum toxin. Can J Neurol Sci 1987; 14 (suppl):533-535

Treating Febrile Seizures

FEBRILE SEIZURES, which occur in about 3% of children between the ages of 3 months and 5 years, often recur (30% to 40%) but are rarely associated with long-term neurologic sequelae or the development of epilepsy or nonfebrile seizures (7% by age 25). The development of nonfebrile seizures later in life occurs more frequently in infants whose febrile seizures are "complex"—that is, focal, prolonged over 30 minutes, or repeated seizures with the same illness—and particularly if these complex features appear in an infant who is already known or thought to have neurological abnormalities. The risk of nonfebrile seizures appearing up to the age of 25 years ranges from 2.4% among children with simple febrile seizures to 49% in the small number having all three complex features.

In a discussion of the treatment of febrile seizures, attention must first be directed to the acute event. Most (95%) febrile seizures are short-lived (less than 30 minutes); 81% are nonrecurrent during a particular febrile illness. Anticon-

vulsant therapy is indicated if the seizures have not stopped before the infant reaches a physician's office or emergency department. Parenteral lorazepam, 0.05 to 0.1 mg per kg body weight, is the antiepileptic drug now preferred by many pediatric neurologists, though the use of parenteral phenobarbital, 10 mg per kg, is still popular. If the seizure is short, then refraining from treating with antiepileptic drugs is acceptable therapy. The infant should then be evaluated for the source of the fever, and the appropriate antipyretic therapy started. The place of routine lumbar puncture in evaluating febrile seizures is debated, but most physicians agree that infants with focal or unilateral seizures, suspicious findings on the physical examination, such as rash or petechiae, hypotension, or grunting respirations, or on a neurologic examination, such as neck stiffness, abnormal tone, an altered level of consciousness, eye deviation, or abnormal fontanel tension, should be tapped. If it is likely that the parents will not comply with follow-up in the next few days, then a lumbar puncture should be considered.

The issue of long-term therapy must be considered in light of the fact that the prophylactic use of antiepileptic drugs, either short- or long-term, will reduce the incidence of recurrent seizures but have no effect on the risk of the later development of nonfebrile seizures. There is also no compelling evidence that febrile seizures per se cause neurologic injury, though some clinicians think that severe or recurrent febrile seizures occur more frequently in children in whom temporal lobe epilepsy ultimately develops. Some physicians advocate instituting the prophylactic use of antiepileptic drugs in so-called high-risk infants, that is, those younger than 12 months, or who have had a previous complex febrile seizure, and those infants with developmental delay, evidence of a neurologic impairment before the seizure, or with temporary neurologic abnormalities after a seizure (Todd's paralysis). None of these factors, however, except for the age at the initial seizure, are major predictors of recurrence. For example, most complex seizures occur as the first seizure and are not predictive of subsequent seizures. These facts certainly support a nontreatment approach to all children with febrile seizures.

Continuous prophylactic therapy has traditionally been accomplished with phenobarbital, though using valproic acid and primidone has also been effective. All of these drugs have substantial and on rare occasions lethal side effects, which has led to the use of intermittent prophylaxis with rectal diazepam. The parenteral solution can be instilled in the rectum at a dose of 0.5 mg per kg (maximum dose 10 mg) at the first sign of a fever or when a seizure occurs. The former approach has been shown by many investigators in Europe and in yet-unpublished studies in this country to reduce the risk of recurring febrile seizures. Administering the drug when the seizure begins, which is now being done with severely epileptic children, reduces the duration of the recurrent seizure and obviates a trip to an emergency department. Side effects are few. The rectal use of lorazepam has also been effective in aborting status epilepticus in epileptic infants and children and will probably become the drug treatment of choice in the intermittent prophylaxis of febrile seizures.

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REFERENCES

Annegers JF, Hauser WA, Shirts SB, et al: Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med 1987; 316:493-498

Joffe A, McCormick M, DeAngelis C: Which children with febrile seizures need lumbar puncture? A decision analysis approach. Am J Dis Child 1983; 137:1153-1156

Knudsen FU: Recurrence risk after first febrile seizure and effect of short term diazepam prophylaxis. Arch Dis Child 1985; 60:1045-1049

Optimal Drug Management of Parkinson's Disease

FOR SEVERAL YEARS A COMBINATION PRODUCT OF CARBIDOPA AND LEVODOPA (Sinemet) has been the principal drug in the treatment of Parkinson's disease. We favor beginning a careful titration of the drug within the first year or two of clearly defined symptoms, at the point when a patient begins to be disabled. This strategem is based on evidence showing that early treatment results in a longer lifespan and that late complications have been related to the progression of the disease and not to the duration of dopa treatment. An opposing claim is that dopa has a finite usefulness and treatment is better postponed until later in the course of the disease.

Sinemet 25-100 (containing 25 mg of carbidopa and 100 mg of levodopa) is typically administered with half a tablet two or three times a day with food, gradually increasing over the next few months to three or four whole tablets a day. If adequate benefits are not achieved by then, switching to Sinemet 25-250 (carbidopa, 25 mg, and levodopa, 250 mg) may be helpful, using half tablets initially and whole tablets subsequently. Each stepwise increase should be given only after a careful evaluation of rigidity, akinesia, tremor, activities of daily living, and possible side effects, particularly dyskinesia and confusion. Patients should be seen every three to four months.

As the duration of disease increases, the efficacy of each dosage may gradually decrease from four or five hours to one or two hours. This "wearing off" can be treated by administering small doses of carbidopa-levodopa at three-, two-, or one-hour intervals during the day and one or more doses at night. The total daily dose should remain constant.

After some years, choreoathetoid dyskinesia may alternate with the wearing-off effect, resulting in a state that fluctuates between reasonably good control, involuntary movements from too much dopa, and parkinsonian akinesia and tremor. This, too, may be treated by shortening the interval between doses or by adding the dopamine agonist, bromocriptine mesylate (Parlodel). The dosage of bromocriptine, 2.5 mg, is begun with a half or a quarter tablet once or twice a day, gradually increasing to 15 to 25 mg a day over several months.

Another approach is to begin therapy in a previously untreated patient with bromocriptine or pergolide mesylate, a new dopamine agonist soon to be available. Eventually, carbidopa-levodopa needs to be added to this regimen, but some neurologists feel that some of the late side effects of dopa may be lessened or postponed by giving dopa-agonist therapy first. A variation on this is to begin therapy with levodopa combined with a dopamine agonist. Rinne, using a mean daily dose of dopa (combined with a dopa-decarboxylase inhibitor) of about 500 mg, plus a mean dose of bromocriptine, 22 mg, found less end-of-dose disturbance and peak-dose dyskinesia at the end of five years than with the use of levodopa alone. It is critical not to begin giving both drugs at the same time. To separate the immediate beneficial and the side effects of the two drugs, we recommend starting with one drug, gradually increasing to the desired dosage, and then doing the same with the second drug.